



Fatty Acid Oxidation (Mitochondrial β oxidation)

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INTENDED LEARNING OBJECTIVES (ILO)

By the end of this lecture the student will be able to:

- 1. List importance of Fatty acid oxidation**
- 2. Illustrate the steps of beta oxidation**
- 3. Discuss role of carnitine in FA oxidation and its clinical implication.**
- 4. Correlate defects in FA oxidation to clinical disorders.**



Importance of fatty acid oxidation

- ❖ It is a very important process supplies most tissues with energy **during fasting state**
- ❖ It is the preferred substrate for **cardiac muscle as a source of energy**
- ❖ It is the vital energy source for **skeletal muscle** during prolonged exercise
- ❖ The brain can not utilize F.A as a source of energy because they **can not cross the blood brain barrier BBB**



- ❖ The brain depends **only on GLUCOSE** for energy production
- ❖ During fasting there is shortage of glucose and the body begins to synthesize endogenous glucose by the process of **GLUCONEOGENESIS for brain metabolism**
- ❖ **GLUCONEOGENESIS** requires energy obtained from F.A oxidation
- ❖ Also F.A oxidation synthesizes ketone bodies in the liver that act as a source of energy for brain and peripheral tissues



Beta (β) oxidation of FA



- **It is the major catabolic pathway of FA**
- **It occurs inside the mitochondria & It involves:**
 - 1. Activation of LCFA (more than 10 carbons) in the cytosol**
 - 2. Transport of LCFA into the mitochondria (Carnitine shuttle)**
 - 3. Steps of oxidation inside the mitochondrial matrix**
 - 4. Calculations of Energetics of FA oxidation**



Activation of LCFA in the cytoplasm utilizing 2 high energy bonds (2 ATP)



fatty acid

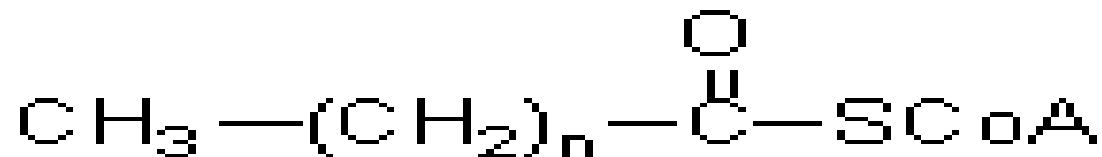


CoASH

ATP

ACYL-CoA SYNTHETASE

THIOKINASE



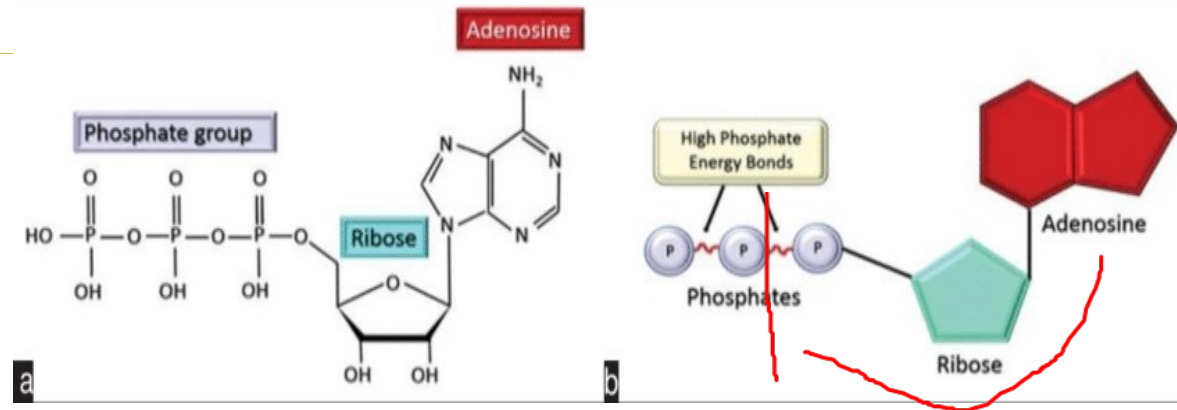
fatty acyl CoA

AMP + PP_i

H₂O

2 x P_i

pyrophosphatase



**The activated FA
needs to go to
the mitochondrial
matrix How?**



**Transport of acyl CoA into
mitochondria through
Carnitine shuttle**



Carnitine shuttle

- Carnitine shuttle allows LCFA **more than 10 carbons** to enter the matrix (as inner mitochondrial membranes are impermeable to CoA).
- FAs **< 10 Carbons** (e.g. FA in milk) passes without the aid of the shuttle. They are activated to their CoA derivatives inside the matrix by matrix



Carnitine shuttle

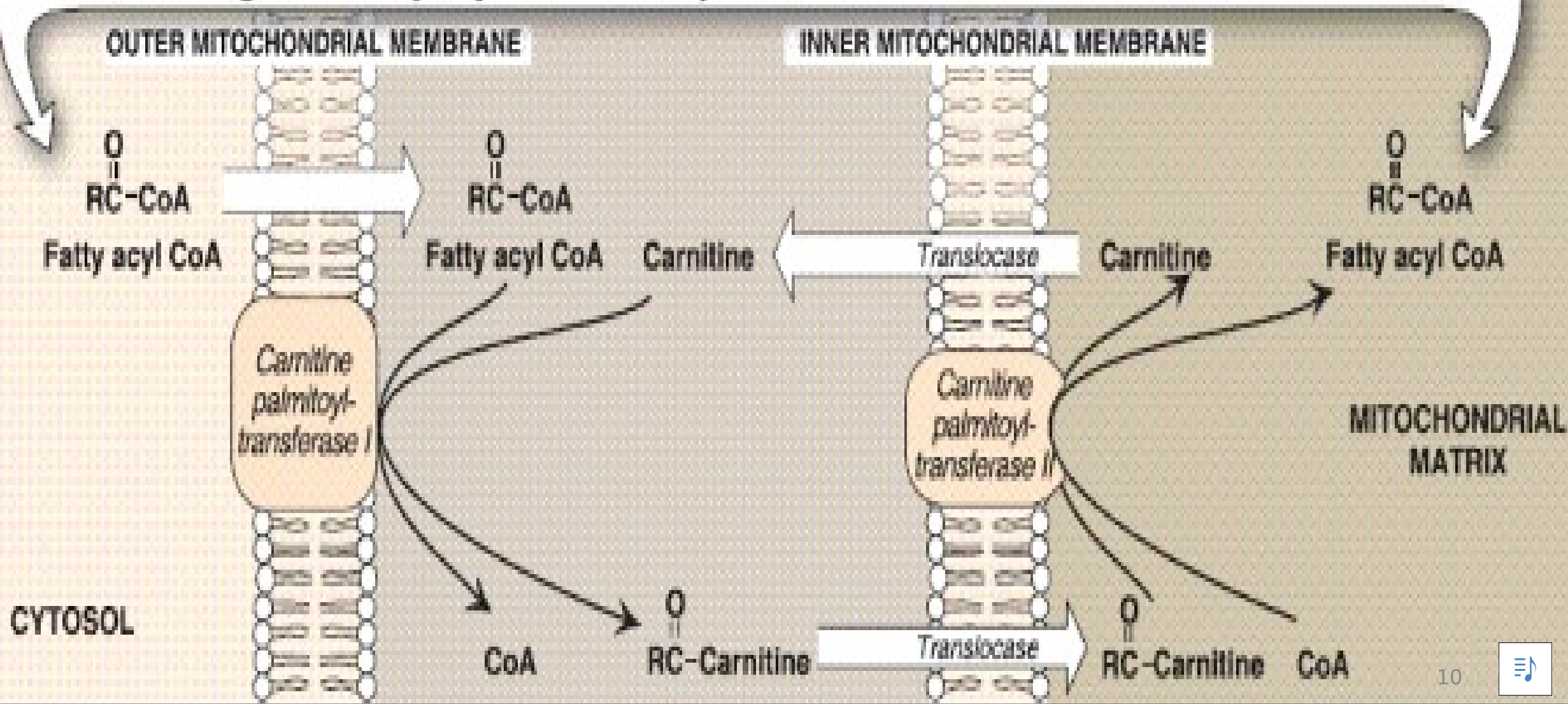
Sources of carnitine:

- 1- **Exogenous from diet (meat products).**
- 2- **Endogenous synthesized carnitine (lysine and methionine) by liver & kidney but not in skeletal or heart muscles.**



Carnitine shuttle

Net effect: Long-chain fatty acyl CoA is transported from the outside to the inside of mitochondria



1- Acyl group transfer

carnitine by

Carnitine shuttle

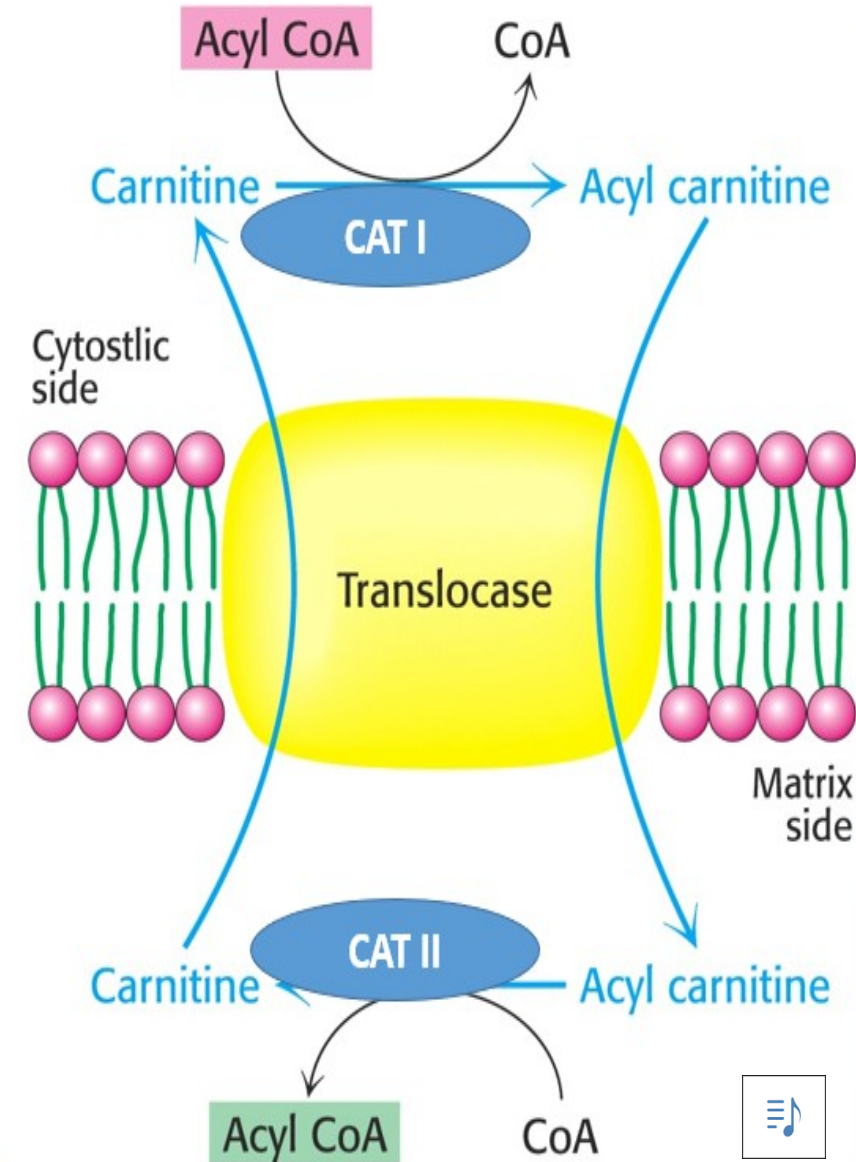


Carnitine Palmitoyl

Transferase I (CPT-I) or Carnitine Acyl Transferase I (CAT-I).

2-Acylcarnitine enters the matrix in exchange for free carnitine by *Translocase*.

3-*(CPT-II, or CAT-II)* catalyzes the transfer of the acyl group from carnitine to CoA in the matrix; regenerating **free carnitine & FATTY ACYL CoA READY FOR**



Carnitine deficiency



Carnitine deficiency results in a **decreased ability of tissues to use LCFA as a source of energy.**

1ry carnitine deficiency:
=Congenital deficiency in any of CPT OR CAT system, during early childhood

CPT-I deficiency (liver)

Inability to use LCFA as a source of energy this impairs Gluconogenesis leading to: severe FASTING hypoketotic hypoglycemia, high level of blood carnitine, hepatomegaly, coma, & death

CPT-II deficiency (cardiac & skeletal ms)

Cardiomyopathy & arrhythmia. Muscle pain (myalgia), Muscle weakness with myoglobinemia & myoglobinuria with red urine following prolonged exercise. damage the kidneys, in some cases leading to life-threatening kidney failure



Carnitine deficiency

**2ry
carnitine
deficiency**

**Malnutrition patients
(vegetarian)**

**Liver disease Patients
(decreased synthesis of carnitine)**

**Hemodialysis patients
(removes carnitine from the blood)**

**Increased requirements for carnitine
(pregnancy, severe infections, burns, or trauma)**

Muscle
weakness,
fatigue,
hepatomegaly,
fasting
hypoglycemia,
coma and death



Carnitine deficiency

Treatment includes:

1. Avoidance of prolonged fasting.
2. Intravenous glucose infusion in hypoglycemia to avoid coma and death
3. Diet high in carbohydrate and low in LCFA, but supplemented with medium-chain fatty acid.
4. In cases of carnitine deficiency, carnitine is given as pills or **CARNITOR (levocarnitine) Injection 1 g per 5 mL vial FOR**

INTRAVENOUS USE ONLY.



key question



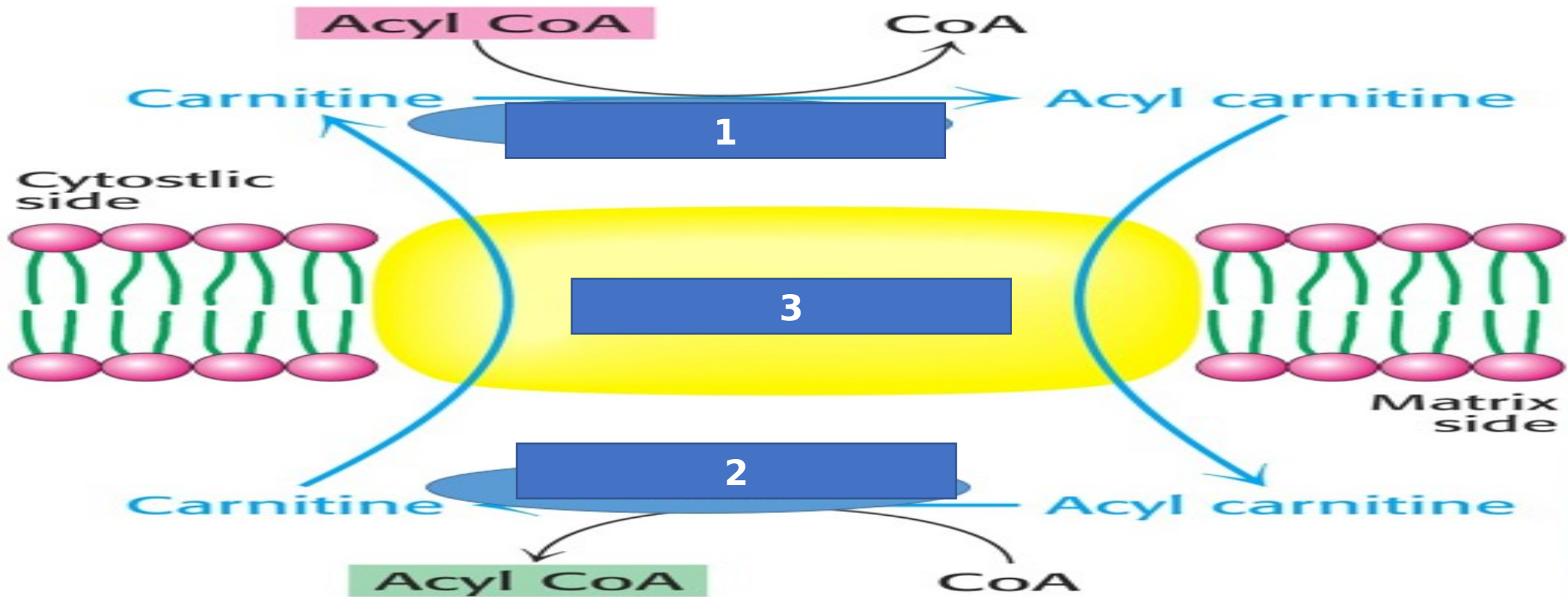
The β oxidation of the fatty acids occurs in which of the following cell organelle?

- A. Cytoplasm**
- B. Mitochondria**
- C. Golgi apparatus**
- D. Endoplasmic reticulum**
- E. Ribosome**

key question



Complete the provided missing labels 1,2,3



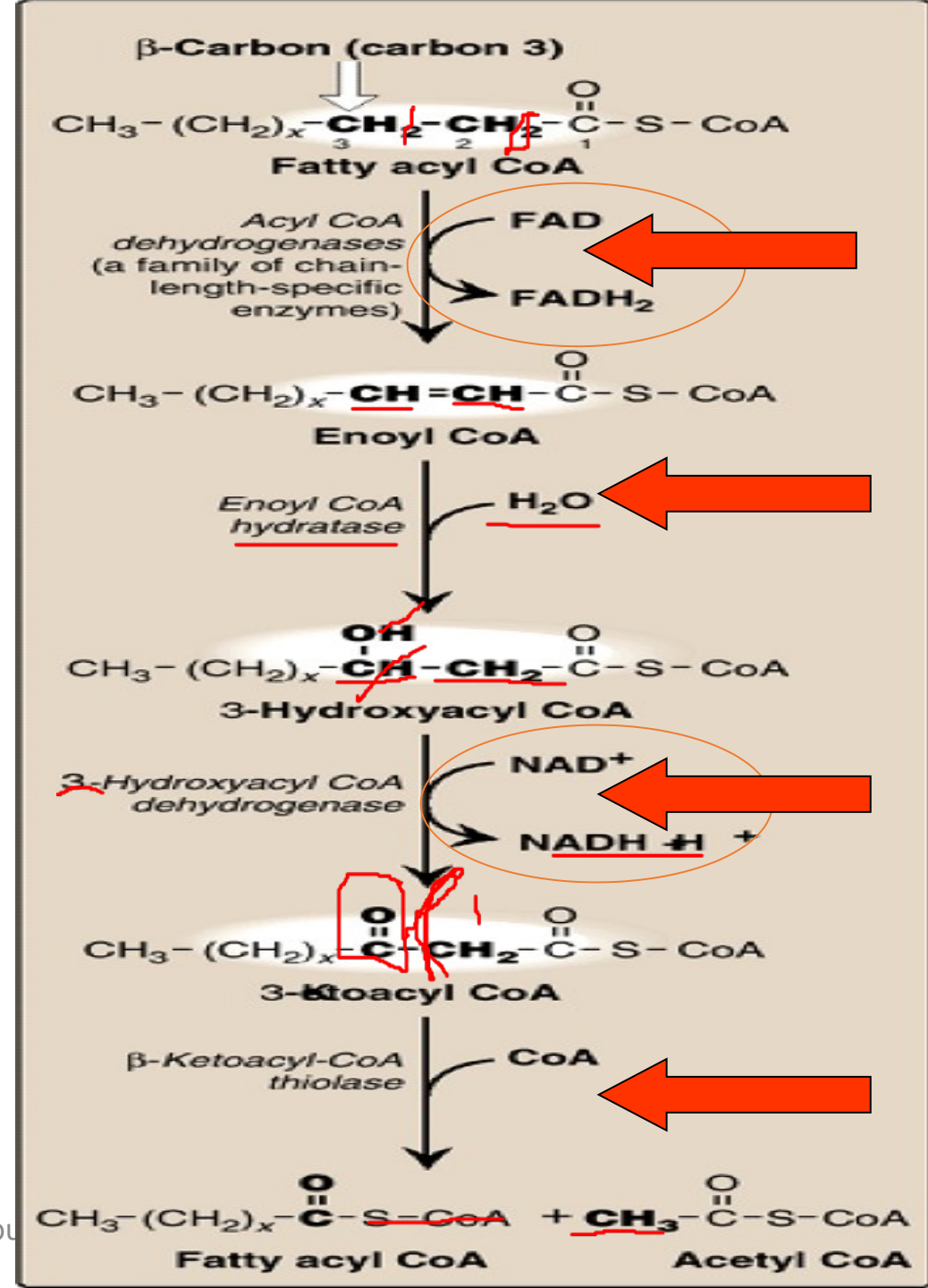
Steps of β -oxidation

Oxidation (FADH₂)

Hydration (add H₂O)

Oxidation (NADH)

Thiolytic cleavage to release acetyl CoA.



Energy yield from fatty acid oxidation



For even saturated FA:

***(number of carbons/2) is the number of acetyl CoA - 1 = Number of cycles. Each Acetyl CoA PRODUCE 12 ATP via Krebs cycle**

***Each cycle generate (NADH+ FADH₂) PRODUCING 5 ATP.**

***[Acetyl CoA is a positive allosteric effector of *pyruvate carboxylase* key enzyme of *gluconeogenesis* thus linking FA oxidation and gluconeogenesis]**



Energy yield from palmitic fatty acid oxidation

The energy yield is high.

E.g.: oxidation of **palmitoyl CoA** to **CO₂** and **H₂O** produces in 7 cycles

8 acetyl CoA + 7 NADH + 7 FADH₂

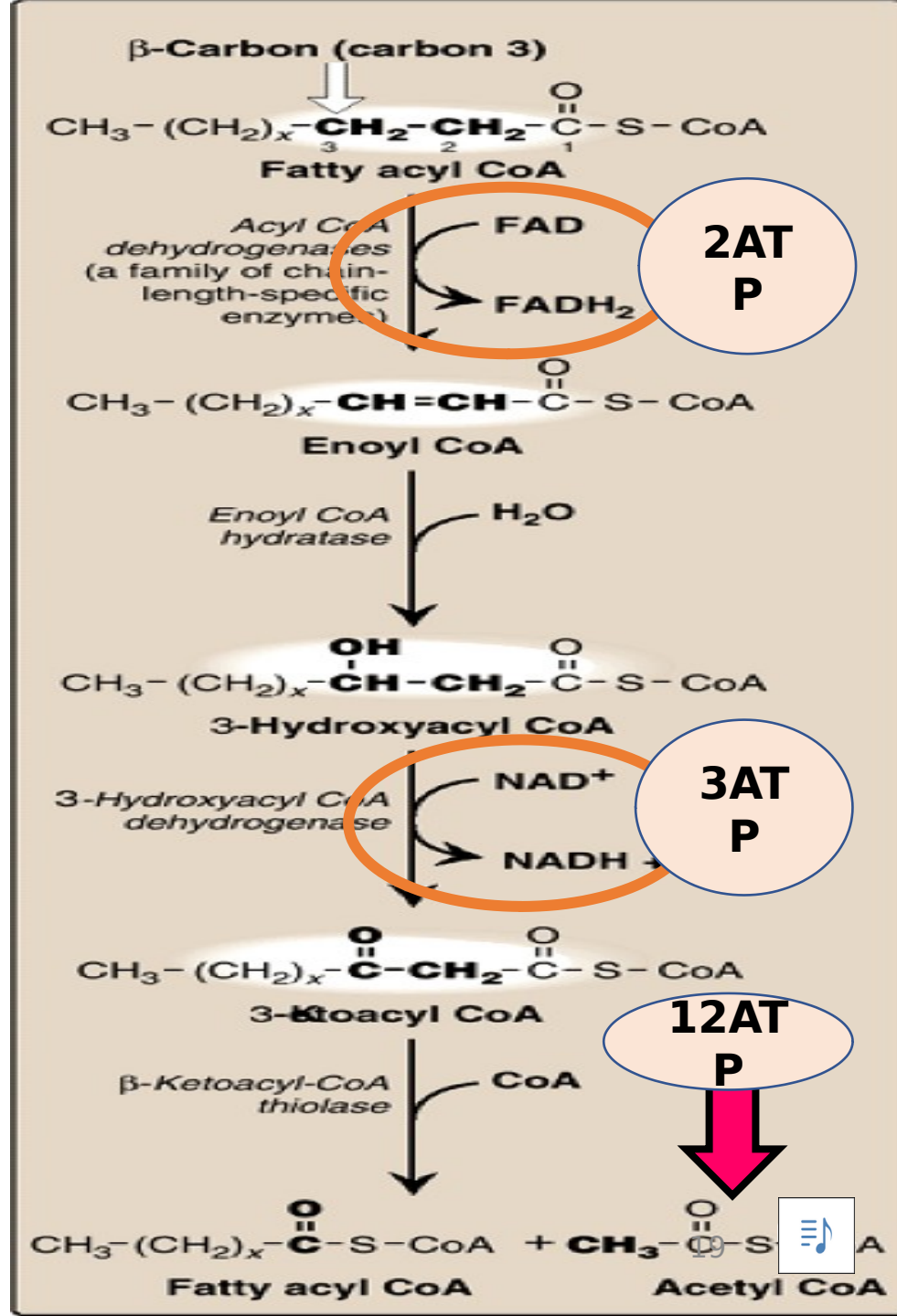
16 carbons/2=8 Acetyl CoA-1= 7 Cycles.

FADH₂=2ATP, NADH=3ATP, 5ATP/cycle via respiratory chain.

7 cycles × 5 ATP = 35 ATP.

8 acetyl CoA × 12 ATP via Krebs cycle = 96 ATP

96 + 35 = 131 ATP - 2 ATP consumed during activation step = **129 FINAL TOTAL ATP**



key question



Calculate energy yield from oxidation of 16 carbon fatty acids

oxidation of 16 carbon fatty acid to CO₂ and H₂O produces in 7 cycles

8 acetyl CoA + 7 NADH + 7 FADH₂

16 carbons/2=8 Acetyl CoA-1= 7 Cycles.

FADH₂=2ATP, NADH=3ATP, 5ATP/cycle via respiratory chain.

7 cycles×5 ATP= 35 ATP.

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96+35=131 ATP-2 ATP consumed during activation step= **129** FINAL TOTAL ATP

Medium-chain fatty acyl CoA dehydrogenase (MCAD) deficiency

- **Inside the mitochondria, there are four fatty acyl CoA dehydrogenase species, each one specific for either short-, medium-, long-, or very-long-chain fatty acids.**
- **MCAD deficiency is one of the most common inborn errors of metabolism, and the most common inborn error of fatty acid oxidation**



Medium-chain fatty acyl CoA dehydrogenase (MCAD) deficiency

- * Is the most common disorder OF fatty acid β -oxidation
- * Fatty acid β -oxidation fuels hepatic ketogenesis, a major source of energy for BRAIN & peripheral tissues after glycogen stores are depleted during prolonged fasting
- (MCAD) deficiency results in decreased ability to oxidize fatty acids with six to ten carbons WITH Elevations of PLASMA acylcarnitine, PLASMA 6-10 hydrocarbon chain fatty acids) & INCREASED URINL



(MCAD) deficiency

- Signs and symptoms appear during infancy or early childhood and include vomiting, lack of energy (lethargy), and hypoketotic (low levels of ketone bodies) hypoglycemia, **HEPATOMEGALLY** due to fatty infiltration, **seizures, coma, and sudden death.**
- Treatment includes high carbohydrate low fat diets and



key question



Which one of the reducing equivalents set is involved in β oxidation of the fatty acids?

- A. NAD & FAD**
- B. NADP & COA**
- C. Lipoic acid & FAD**
- D. NADP & FAD**
- E. Lipoic acid & FAD**

key points



- 1.The importance of Fatty acid oxidation**
- 2.Steps of beta oxidation**
- 3.Role of carnitine in FA oxidation and its clinical implication.**
- 4.Defects in FA oxidation to clinical disorders as (MCAD) deficiency.**

SUGGESTED TEXTBOOKS



1. "Lippincott's Illustrated Reviews in Biochemistry" by P.C.Champe, R.A.Harvey and D.R. Ferrier.
2. "Harper's Biochemistry" by R.K.Murray, D.K.Granner, P.A. Mayes and V.W. Rodwell.

Thank
you

